Lessons From SUPPORT:

Ethical Implications for Research on Medical Practices

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“The parental consent dilemma: Saving extremely premature babies by signing forms” - Kelly Benham, Oct 18, 2013, Tampa Bay Times

“All babies born so young are experiments. The rest is just paperwork”

“Had I been asked, I probably would have signed her up for a research study. If things had gone well, I might have believed the study had helped. If things had gone poorly, I might have blamed the study and feared I'd been duped.”
Oxygen and Preterm Infants

• 1950s:
  • Unrestricted supplemental oxygen decreased death but increased retinopathy and blindness

• 1960s:
  • Neonatologists restricted oxygen to 50% or less – resulted in 16 deaths per case of blindness prevented

• 1980s-1990s
  • Pulse oximetry used to target oxygen saturations between 85-95%
SUrfactant Positive airway pressure and Pulse Oximetry Trial

- 2005-2009
- Sponsored by NICHD Neonatal Research Network
- Eligibility: 24 to 28 weeks
- Factorial Randomization:
**SUrfactant Positive airway pressure and Pulse Oximetry Trial**

- **Oxygen Saturation:** 85-89% vs 91-95%
  - Oximeters altered ±3% to read 88-92% for both groups for blinding
  - Oximeters were accurate for sats <85% or >95%
- **Composite Primary Outcome:**
  - Severe Retinopathy or Death
- **Hypothesis:**
  - Lower target oxygen-saturation range will reduce composite outcome
Target Ranges of Oxygen Saturation in Extremely Preterm Infants

• The rate of the composite primary outcome, severe retinopathy or death, did not differ significantly between the groups

  • Severe retinopathy
    • 8.6% in the low oxygen group versus
    • 17.9% in the high oxygen group [p<0.001]
    • Number needed to treat = 11

  • Death before discharge
    • 19.9% in the low oxygen group versus
    • 16.2% in the high oxygen group [p=0.04]
    • Number needed to harm = 27
Kaplan-Meier Estimate of Survival to Hospital Discharge, Transfer, or 1 Year of Life

(hazard ratio, 1.28; 95% CI, 0.98 to 1.68; P=0.07)
Actual Median Oxygen Saturation with Oxygen Supplementation in the Two Treatment Groups
SUPPORT Conclusions

• “Lower target oxygen range increased risk of death and reduced risk of severe retinopathy among survivors.”

• “At the present time, caution should be exercised regarding a strategy of targeting levels of oxygen saturation in the low range for preterm infants, since it may lead to increased mortality.”
SUPPORT and Informed Consent

• Consent obtained during prior to premature labor
  • Process required 1.8-3.6 hours per enrolled infant
    • 50% of parents approached gave permission
    • 50% of these delivered and were enrolled
  • Non-enrolled babies were lower SES, more likely African-American, potentially at higher risk for premature labor
  • Babies not enrolled in study had poorer outcomes than babies in either enrolled group

• Review and Oversight:
  • Study approved by 23 IRBs
  • Independent Data and Safety Monitoring Board reviewed the primary outcomes, adverse events, and interim results
SUPPORT and Informed Consent

- “Sometimes higher ranges are used and sometimes lower ranges are used. All of them are acceptable ranges. In this part of the study we would like to pinpoint the exact range that should be used to prevent some of the problems that occur with premature babies such as Retinopathy of Prematurity (ROP).” (UAB)

- “Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby.... There may be benefits to your child directly, including a possible decrease in chronic lung disease (need for extra oxygen near discharge) and/or a decrease in the need for eye surgery as a result of exposure to oxygen.” (UCSD)
Determination:

- The investigators **incorrectly** believed that because all infants were randomized to oxygen levels within the standard range it follows that the study involved **no more than minimal risk**.
- The **risks of the randomization** made it more likely that there would be differences in the outcomes of the two groups including death, neurologic problems and ROP.
- The informed consent form does not adequately describe **any reasonable and foreseeable risks**. The form should have explained that the study involved substantial risks.

Required Action:

- Provide a plan that the IRB will use to ensure that improved informed consent documents include and adequately address the basic elements of informed consent.
An Ethical Breakdown

• The Editorial Board, April 15, 2013

• “23 academic institutions authorized a research project that failed to meet the most basic standard: providing an informed consent document to parents that accurately described the risks and benefits of the research to be conducted on extremely premature babies. This failure was startling and deplorable.”
Why I got engaged by SUPPORT

• What I was reading in the press seemed to simplify complicated ethical, clinical and scientific issues

• As a pediatric pulmonologist, I did not think that children in SUPPORT were substantially harmed by their participation

• As a bioethics scholar, I appreciated that efforts to support parental understanding and decision-making for research are hard to do well

• As a past IRB chair, I appreciated the challenges of providing meaningful and appropriate oversight
The OHRP and SUPPORT

“Furthermore, the conclusion of OHRP overreaches. Although we acknowledge that the permission forms could have been improved, we disagree that the random assignment of infants imposed additional risks that the investigators failed to disclose.”

Wilfond BS, Magnus D, et al., June 20, 2013 (with 46 signatories)

The OHRP and SUPPORT- Another View

“Given the seriously deficient nature of the consent documents, the determination of the OHRP on March 7, 2013, was justified and did not overreach.”

OHRP Public Hearing on August 28, 2013

- An unprecedented event
- 27 presenters
- 7 minutes followed by 5 minutes of questions from NIH, OHRP, and FDA

- [http://www.hhs.gov/ohrp/index.html](http://www.hhs.gov/ohrp/index.html)
- George Annas, Lois Shepard, John Lantos, Nancy Kass, Steve Joffe, Elisa Hurley, Robert Platt were highlights
OHRP Public Hearing on August 28, 2013

• I gave a presentation based on CTSA Consortium Ethics/Pediatrics discussions about what we can learn from:
  • The “Quality Improvement Movement” to consider the role for OHRP
  • The Wisconsin Cystic Fibrosis Newborn Screening Trial to consider issues related to risks or randomization and waiver of consent
Wisconsin Cystic Fibrosis Newborn Screening Study

- 1985-1994: 650,000 infants enrolled in a randomized clinical trial of cystic fibrosis newborn screening
  - Results returned in 6 weeks or in 4 years
  - All infants with CF were treated using standard care approaches
- NIH, IRBs, Cystic Fibrosis Foundation, community review:
  - Waiver of informed consent was appropriate
  - Efforts made to disclose screening and allow parents access to results
- Outcome:
  - Early detection improved nutritional status
  - Early detection increased chance of early Pseudomonas acquisition
  - A 2004 CDC Workshop concluded that CF NBS was justified
Late at night, and without permission, Reuben would often enter the nursery and conduct experiments in static electricity.
Questions to Consider

1. Is there a clear **meaning** for the phrase "standard of care," and if so, what is it?
2. What criteria are appropriate for determining which **risks** are "reasonably foreseeable?"
3. What must be **disclosed** in consent documents for comparative effectiveness research?
4. How far does the **authority** of the OHRP extend in its role of protecting the rights and welfare of human subjects of research?"
Is there a clear **meaning** for the phrase "standard of care," and if so, what is it?

- SUPPORT consent forms referred to “standard of care” and OHRP referred to “standard of care” research
  - “standard of care” is a legal term, not a clinical term
  - The best term to describe these activities is not clear

### Care Concepts
- Routine care
- Usual care
- Standard care
- Clinical Standard Work

### Research Concepts
- Quality Improvement
- Patient Oriented Outcomes Research
- Comparative Effectiveness Research
- Learning Health Systems

- **Research on Medical Practices:**
  Collect (and share) clinical information.....
  about the impact of typical clinical practices on health outcomes.........
  to improve future practice  directly within a health system and by others
The underlying challenge of medical practice

- Wide practice variation for many tests, treatments, etc.
  - Clinicians, clinical groups, institutions
- Often, no conclusive data that one approach is better
- Or, available data does not guide routine practice
What criteria are appropriate for determining which risks are "reasonably foreseeable"?

1. Lack of evidence to suggest specific events are expected:
   - Impact of oxygen saturation targets on death was not foreseen prior to this study based on other clinical studies

2. Measurement of death in a protocol is not determinative
   - Death was part of composite endpoint to avoid underestimation of the risk of ROP, since ROP can’t be determined in children who die
     - Measuring death does not mean it is risk of the research
     - Expected and serious risk of many clinical contexts
       - Death was measured in the CF NBS studies

3. Related to research activities
   - Death was a foreseeable risk of being an extremely premature infant
Risks of Comparative Effectiveness Research

Feudtner, Schreiner, and Lantos describe 9 types of risks.

*NEJM.* 2013 369:892-4

1. Risks (and benefits) of intervention A as compared with intervention B
2. Due to randomization
3. Associated with being in the trial as compared with not being in it
   - All do not cause a net increase in risk compared to usual care though individual experiences may be different
   - Could be “minimal risk” and consent “waived” in current regulatory framework?
   - Does not mean not disclosed
What must be **disclosed** in consent documents for comparative effectiveness research?

- Often consent forms are expected to do too much and as a result do too little
- SUPPORT points out better efforts to convey goals of research, risks of clinical care, and alternatives are needed
  - A serious systems issue
  - Not an additional paragraph in a 10 page form
- **Innovative** approaches are needed to help
  - **Individuals** understand specific research projects so they make a decision
  - **Communities** consider when research activities are appropriate for “waivers of informed consent”
Parents randomly allocated one page information leaflets about a hypothetical study of neonatal pain relief understood it better than parents allocated six page leaflets.

Parents randomly allocated to receive an added verbal explanation, with opportunity for questions, understood the study even more.
Helping individuals to decide whether to join a research study

- Goal - help individuals make a decision appropriate with their values and interests
  - Not only about risks

- Keep information focused and brief to promote understanding
  - Contextualized from clinical context
  - Use brochures, graphics, video, websites, in person conversation, etc

- “Supplemental information” should available about what:
  - All participants need to know after they join *this* study
  - All participants should know before they decide about any study
  - Some participants might want to know to decide about this study
  - Lawyers might want to know
How far does the authority of the OHRP extend in its role of protecting the rights and welfare of human subjects of research?

- The permission forms used in SUPPORT were not ideal
- OHRP has a role in the substantive enforcement of the regulations, but
  - Needs to be limited to contexts where there is a clear consensus about errors of substantive judgment by IRBs
  - Need to be mechanisms for appeal (as in other regulatory contexts)
- OHRP should seek out expert opinion on complex ethical and clinical issues and encourage further public dialogue
- OHRP should not issue findings against investigators when there is broad disagreement about the substantive issues about risks and interpretations
- **OHRP did the right thing to engage in further discussion**
Assessing public attitudes

• Public willingness to support research and health care integration is necessary

• The role of public attitudes in policy decisions is complicated

• Difficult to convey the issues effectively to elicit meaningful responses
“Attitudes about the Ethics of Research on Medical Practices” (ROMP)

- Objective: understand how the public views ethical implications of randomization within usual practices
- NCATS award to CTSAs at Stanford (SPECTRUM) and Seattle (ITHS)
- Development of videos and illustrations to convey
  - Influences on practice variation
  - Research on medical practice
  - Information disclosure

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The last word, for now...

- The risks of standard treatments are NOT risks of research
  - Research comparing two standard treatments is the best way to identify the risks of the clinical interventions
- We need better approaches for informed consent processes
  - Focused on helping prospective participants truly understand the most crucial elements of research and clinical practice
- Sometimes consent can be “waived”
  - Requires active and innovative community engagement and alternative ways to reach patients
- Empirical social science research is needed
  - Public, provider, researcher, regulator attitudes and understanding
  - Novel approaches to improve informed consent and to engage patients and communities